Endocrine hypertension

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- **Idiopathic hypertension** (primary or essential) - 85%

- **Secondary hypertension -** identifiable conditions - 15%:
  - primary renal disease
  - oral contraceptive use
  - sleep apnea syndrome
  - congenital or acquired cardiovascular disease (i.e. coarctation of the aorta)
  - **excess hormonal secretion**

- **Endocrine Hypertension -** states in which hormonal derangements result in clinically significant hypertension:

1. diseases of adrenal cortex and medulla
2. hyper- and hypothyroidism
3. primary hyperparathyroidism
4. acromegaly
5. obesity, insulin resistance (metabolic syndrome)
6. oral contraceptives use
7. renin secreting tumors

Hypertension of adrenal origin

- Primary aldosteronism
- Cushing's syndrome
- Pheochromocytoma
- Syndromes due to excess deoxycorticosterone production
- Type II pseudohypoaldosteronism (Arnold-Healy-Gordon Syndrome)
- Androgen- & estrogen-producing adrenal tumors
- Primary cortisol resistance

Primary aldosteronism

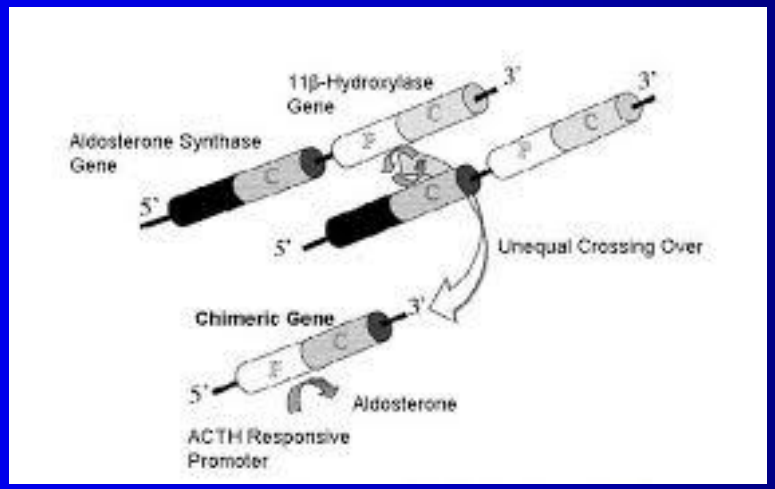
- prevalence: previously - 1-2%, recent data – 4-10%
- sporadic or familial
- **adenoma** (Conn's syndrome): 30-40%
- **hyperplasia** (uni- or bilateral) of zona glomerulosa tissue: 60%
- aldosterone-producing adrenocortical **carcinoma: 0.5-1%**
- dexamethasone (glucocorticoid)-remediable aldosteronism: **1-3%**
- ectopic secretion (ovarian, renal and intestinal carcinoma) **< 1%**

Primary aldosteronism - causes

1. **Aldosterone-producing adenoma (APA)-** small (usually < 2 cm), more common in women
2. **Bilateral adrenal hyperplasia (BAH) –**idiopathic, milder extent of hyperaldosteronism, degree of hypokalemia and suppression of PRA compared to APA
3. **Unilateral adrenal hyperplasia (UAH) -** hypertension and biochemical abnormalities may be cured or ameliorated by unilateral adrenalectomy (similar to APA)
4. **Adrenal carcinomas –** rare, usually large tumor (> 5 cm), the diagnosis based upon evidence of extension of the tumor through the adrenal capsule or a high mitotic index on histologic examination

Primary aldosteronism - causes

- **Familial aldosteronism** (2%)
  - **<u>familial hyperaldosteronism type 1</u>**: glucocorticoid-remediable (GRA), autosomal dominant disorder - chimeric gene duplication: 5'-promotor region of the 11 β-hydroxylase gene (regulated by ACTH) + coding sequences of the aldosterone synthase gene
  - regulation of aldosterone synthesis by ACTH



Primary aldosteronism - causes

- should be considered in patients with:
  - early-onset hypertension
  - suppressed PRA
  - strong family history of early cerebral hemorrhage (< 35 yr)

- <u>diagnosis of GRA:</u>

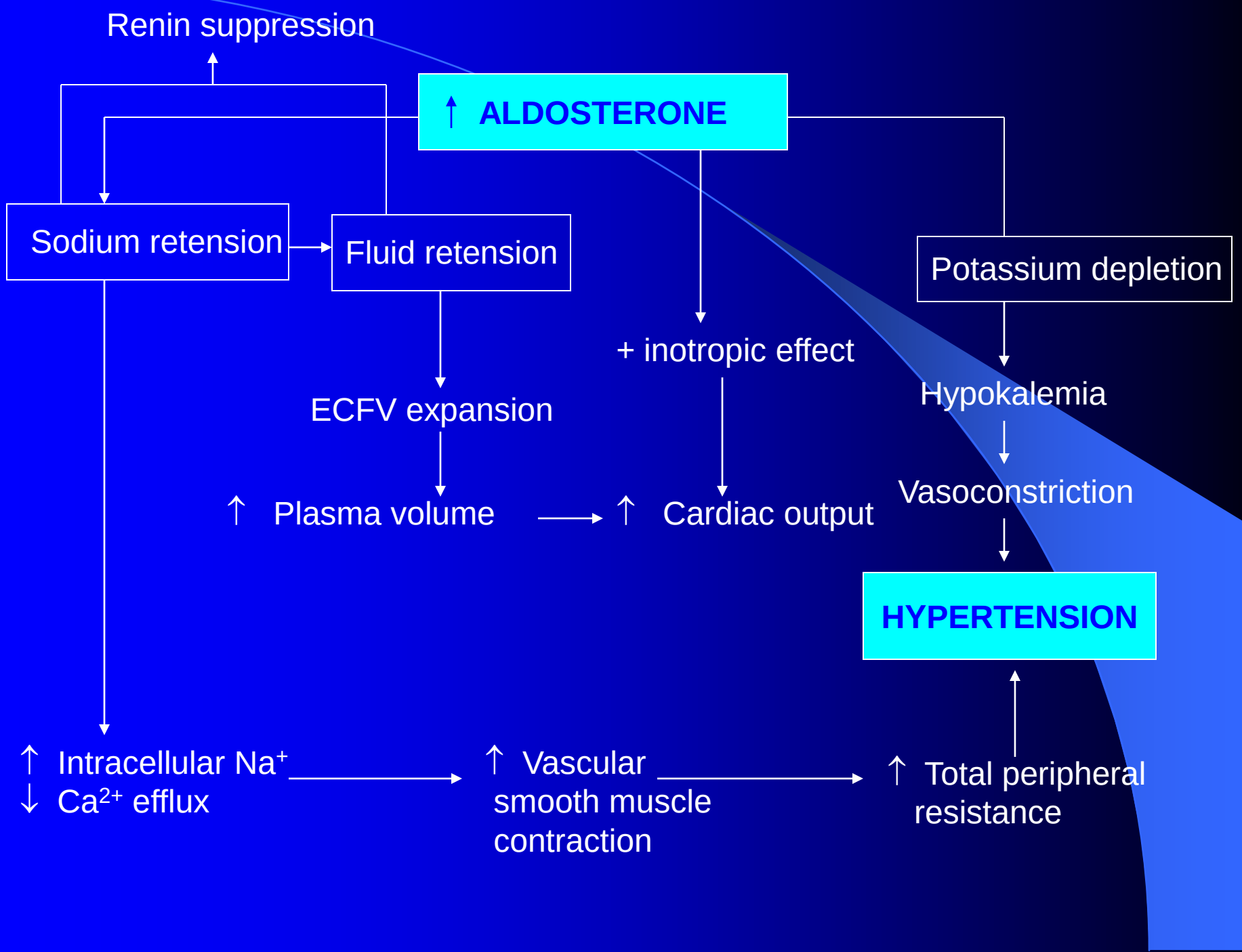
→ suppression of serum aldosterone (dexamethasone 0.5 mg each 6 h for 48 h - reduction of aldosterone to undetectable levels (< 4 ng/dl))

→ genetic testing

- <u>treatment</u> - dexamethasone

- **<u>familial hyperaldosteronism type 2</u>:**

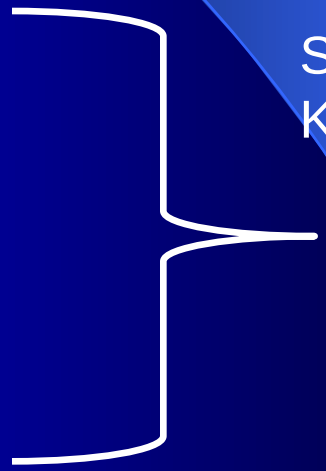
  - not glucocorticoid remediable
  - responsible gene has been linked to chromosome 7p22 but has not yet been identified
  - present in at least two relatives


Renin suppression
↑ ALDOSTERONE
Sodium retension
Fluid retension
Potassium depletion
+ inotropic effect
ECFV expansion
Hypokalemia
↑ Plasma volume
↑ Cardiac output
Vasoconstriction
HYPERTENSION
↑ Intracellular Na+
↓ Ca2+ efflux
↑ Vascular smooth muscle contraction
↑ Total peripheral resistance

Hyperaldosteronism - clinical features

- hypertension (severe)
- hypokalemia (< 3.5 mEq/l), alkalosis

- fatigue, weakness
- ↑ thirst
- polyuria (especially nocturnal)
- paresthesias
- headaches



Symptoms of K^+ depletion

Primary hyperaldosteronism - diagnosis

- biochemical assays: ↓K^+ (< 3.5 mEq/l), ↑K^+ in urine (> 50 mmol/24h)

  up to 20% of patients may have normal or low-normal serum K^+ concentrations!!!

- hormonal assays: aldosterone and plasma renin activity before and after 2 hours in the upright posture (activation of renin system with ↑aldosterone)

  in case of adenoma – no significant change or ↓aldosterone

- 24-hour urine collection for aldosterone (>20 μg/24h)
- aldosterone (PA, ng/dL) to renin activity (PRA, ng/ml/h) ratio:

  - < 20 - normotensive or essential hypertension
  - > 20 - suspicion for primary aldosteronism
  - > 30 (with a PA ≥ 15 ng/dl) - 90% sensitivity and 91% specificity for the diagnosis of primary aldosteronism
  - ≥ 50 - diagnostic of primary aldosteronism

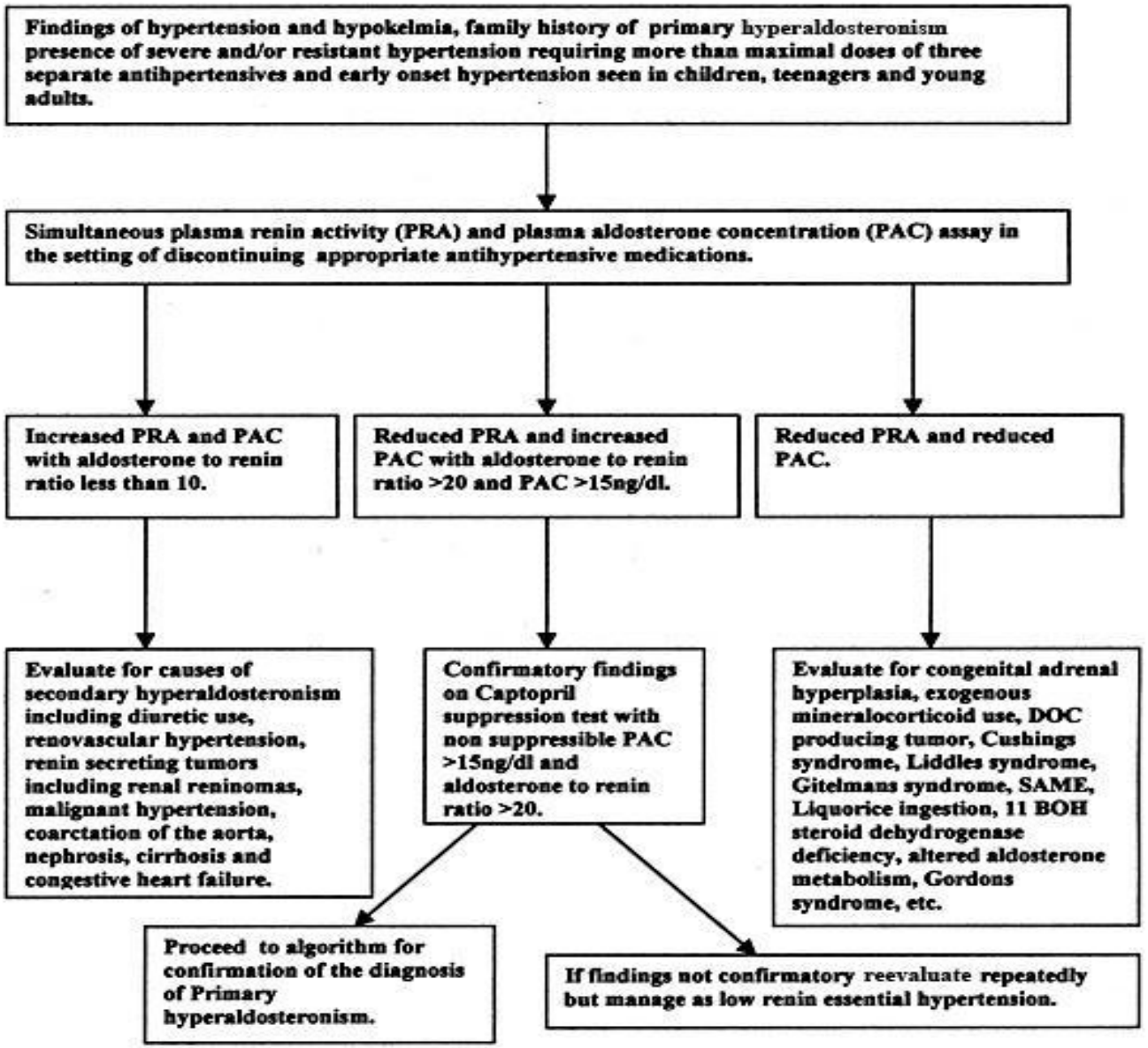
- the best radiographic procedure: adrenal CT scanning
- adrenal vein sampling -‘gold standard’ in diagnosis of unilateral versus bilateral aldosterone hypersecretion
- US – less sensitive
- MRI, adrenal scintigraphy – second choice diagnostic tools

Primary hyperaldosteronism - treatment

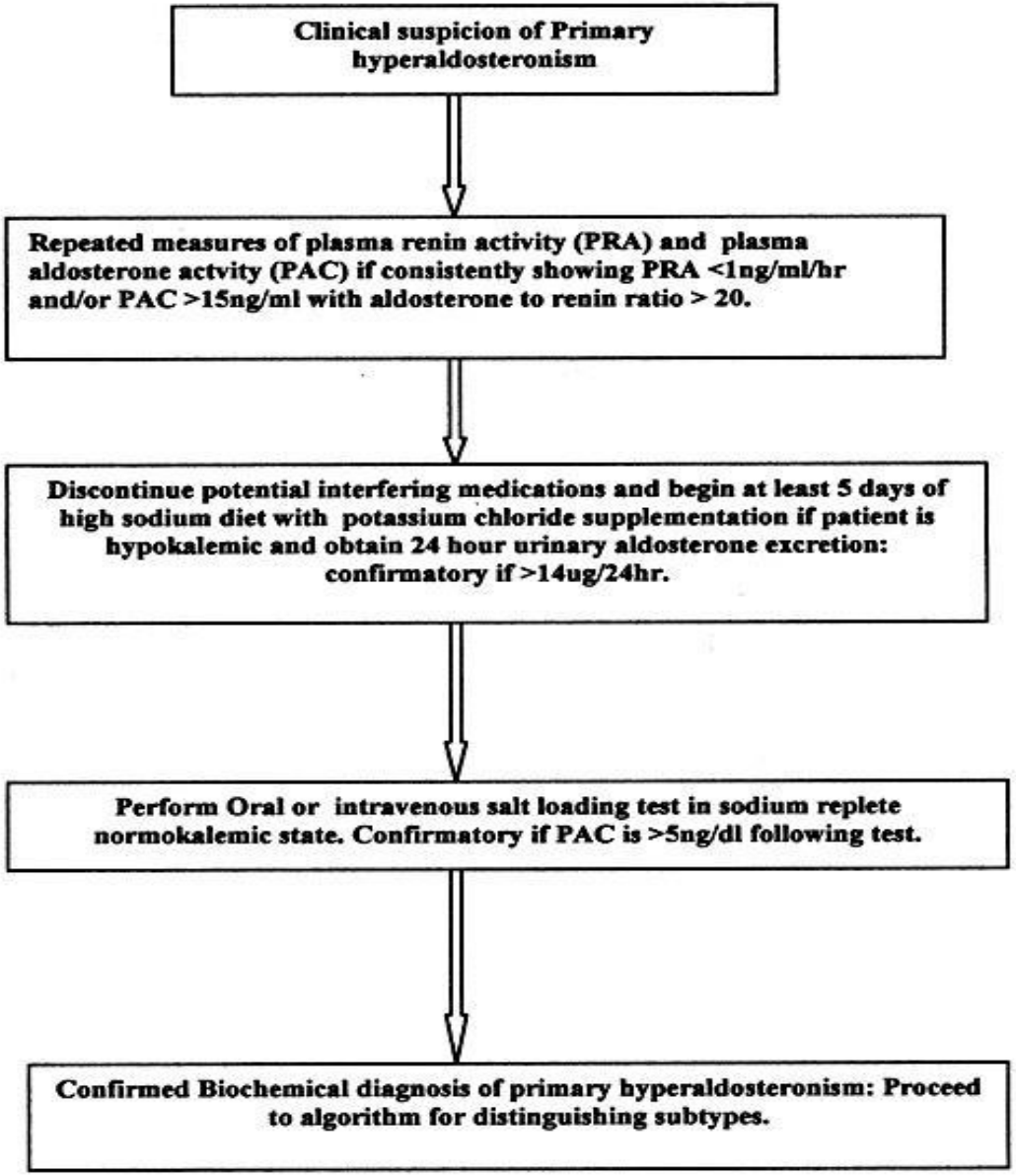
- adenoma - surgery (often laporoscopic) *resection of APA may cure or ameliorate hypertension in APA patients and reverse the hypokalemia*
- bilateral adrenal hyperplasia - mineralocorticoid receptor antagonist – eplerenone (2 x 25 mg) or spironolactone (100-500 mg)

- **spironolactone**: 50-400 mg/day, usually 2x/day, side effects (at doses >100 mg/day) - especially in males (gynecomastia and erectile dysfunction) and females (menstrual dysfunction)
- **eplerenone** - no anti-androgen activity
- **dihydropyridine calcium channel antagonists** - effectively ↓ blood pressure and may ↓ aldosterone secretion
- dietary sodium restriction (<100 mmol/day), regular aerobic exercise, maintenance of ideal body weight

Algorithm for identification and screening of possible primary hyperaldosteronism



Algorithm for confirmation of diagnosis of Primary Hyperaldosteronism



Pheochromocytoma

- catecholamine-producing tumors of chromaffin cells
- WHO classification:
  - intra-adrenal paragangliomas (85%) - **pheochromocytomas**
  - extra-adrenal paragangliomas (15%)
    - ✓ from sympathetic nervous system-associated chromaffin tissue
    - ✓ from parasympathetic nervous system-associated chromaffin tissue

Pheochromocytoma

- present at any age (more commonly in the 4-5th decades)
- located in **adrenals** - 90% in adults, 70% in children
- unilateral - 90% – more frequent in the right adrenal (65% vs. 35%)
- bilateral – 10% in adults, 35% in children, (common in familial syndromes)

Chromaffin paragangliomas

- extra-adrenal tumors arising from sympathetic ganglia
- 10% of chromaffin-tissue tumors in adults, 30% in children
- 36-60% - functional, secreting norepinephrine, normetanephrine
- 70% - intra-abdominal (juxtarenal, para-aortic region, bladder)
- 30% - chest (anterior or posterior mediastinum, heart)

Pheochromocytoma - clinical presentation

Hypertension	>98%
Hypertension sustained	50-60%
Hypertension paroxysmal	50%
Headache	70-90%
Palpitations+tachycardia	50-70%
Diaphoresis	60-70%
Fever	>66%
Pallor	30-60%
Hyperglycemia	42%
Abdominal/chest pain	20-50%
Nervousness	35-40%
Anxiety	20%
Nausea	26-43%
Vomiting	26-43%
Fatigue	15-40%
Flushing	18%
Orthostatic hypotension	12%

- Headaches + palpitations + sweating in patient with hypertension – suspicion for a pheochromocytoma

- ***Attacks of signs*** precipitated by: palpation of the tumor, postural changes, exertion, anxiety, trauma, pain, ingestion of foods or beverages containing tyramine (certain cheese, beer, wine), use of certain drugs (histamine, glucagon, phenothiazine, metoclopramide), intubation, induction of anesthesia, chemotherapy, endoscopy, catheterization, micturition or bladder distension (in case of bladder tumors)

Pheochromocytoma/paraganglioma - secreted substances

- adrenal pheochromocytomas - mainly epinephrine
- extra-adrenal paragangliomas - norepinephrine
- serum level of catecholamines does not correlate with tumor size!!!
- neuropeptide Y – very potent vasoconstrictor
- neuron-specific enolase (NSE) – elevated in about 50% of patients with malignant pheochromocytoma
- other peptides: PTHrP, ACTH, erythropoietin, IL-6, CgA, adrenomedullin

Malignant pheochromocytoma

- 15% of pheochromocytomas

- <u>functional metastases:</u>
- to the skull – common, palpable
- to the ribs – chest pain
- to the spine – back pain, neurologic symptoms
- pulmonary and mediastinal metastases – dyspnea, hemoptysis, pleural effusion, Horner's syndrome
- to the thoracic duct – chylothorax
- to the liver – hepatomegaly
- in mesenteric nodes

Genetic syndromes associated with pheochromocytomas & paragangliomas

- 20-30% of pheochromocytomas or paragangliomas

- <u>recommendations for genetic screening:</u>
- *extraadrenal paragangliomas*
- *multifocal tumors*
- *onset of symptoms at a young age (< 50)*
- *family history of such tumors*
- *patients with other manifestations of familial syndromes*

Multiple endocrine neoplasia type 2 (MEN2)

- autosomal dominant
- mutations in *RET* protooncogene on chromosome 10 (encoding a transmembrane receptor tyrosine kinase)
  - MEN2A (90%)
  - MEN2B (10%)

- in both types – pheochromocytomas develop in adrenals, 4% - metastatic, usually bilateral

MEN2A (Sipple's syndrome)

- medullary thyroid carcinoma (95-100%)
- hyperparathyroidism (multiglandular hyperplasia – 35%)
- pheochromocytoma (50%) – often in middle age
- high incidence of lichen planus amyloidosis and Hirschprung's disease

MEN2B

- medullary thyroid carcinoma (more aggressive and at earlier age than in MEN2A)
- mucosal neuromas
- intestinal ganglioneuromas
- marfanoid habitus
- pheochromocytoma
- hyperparathyroidism – absent!

Von Hippel-Lindau Disease (VHL)

- autosomal dominant
- tumors in multiple tissues:
- **pheochromocytomas (only in type 2 VHL)**
- hemangioblastomas in the retina, cerebellum, spinal cord
- renal cysts
- renal clear-cell carcinoma
- cysts in pancreas
- endolymphatic sac tumors (vertigo, hearing loss, ataxia)
- adnexal cystadenomas
- epididymal cystadenomas

- **pheochromocytomas in VHL2:** at an early age (mean 28 years), bilateral, produce only epinephrine

- type 2A VHL:

  hemangioblastomas + pheochromocytomas, low risk for developing renal cell carcinomas

- type 2B VHL:
- hemangioblastomas + pheochromocytomas, high risk for developing renal cell carcinomas

- type 2C VHL:
- pheochromocytomas, no hemangioblastomas or renal cell carcinomas

von Recklinghausen's neurofibromatosis type 1 (NF-1)

- autosomal dominant
- mutation in the NF-1 tumor suppressor gene
- optic gliomas, plexiform neurofibromas, subcutaneous neurofibromas, schwannomas of cranial and vertebral nerve roots, hypothalamic hamartomas, skeletal abnormalities
- high risk of developing malignant peripheral nerve sheath tumors and leukemia
- multiple cutaneous pigmented cafe au lait spots (usually more then 6 spots > 1.5 cm)

Pheochromocytomas in NF-1

- 0.1-5.7% of patients
- similar to sporadic pheochromocytomas:
  - 84% - solitary adrenal tumors
  - 10% - bilateral
  - 6% - extra-adrenal paragangliomas
  - 12% - metastases or local invasion
- mean age at diagnosis – 42 years

Familial paraganglioma/pheochromocytoma syndrome

- autosomal dominant
- mutations in genes encoding mitochondrial complex II
- multicentric head/neck paragangliomas, sympathetic paragangliomas, adrenal pheochromocytomas

Pheochromocytoma - diagnosis

- **24-h urine collection for metanephrines**
- metanephrines in plasma
- plasma or urine free catecholamines (less sensitive and specific)
- ultrasound scanning
- metaiodobenzylguanidine (MIBG) scintigraphy
- CT and MRI imaging
- positron emission tomography (PET) scanning
- somatostatin receptor imaging with ^{111}In-Octreotide
- venous sampling for catecholamines

Pheochromocytoma - treatment

- **preoperative management**:

- calcium channel blockers
- alpha-adrenergic blockers
- ACE inhibitors
- beta-adrenergic blockers (not prescribed without alpha-blockers)
- metyrosine

Pheochromocytoma - surgical management

- patients should be normotensive, well-hydrated
- monitoring during surgery: blood pressure, ECG

- laparoscopy
- needlescopic adrenalectomy
- adrenal cortex-sparing surgery
- open laparotomy

Syndromes due to excess deoxycorticosterone (DOC) production

- DOC – second most important mineralocorticosteroid hormone
- excess DOC should be suspected in any hypertensive patient with hypokalemia and suppression of renin and aldosterone production

Syndromes due to excess DOC production

- 17α-hydroxylase deficiency
- 11β-hydroxylase deficiency
- androgen- and estrogen-producing adrenal tumors
- primary cortisol resistance

17α-hydroxylase deficiency

- single gene mutation
- impaired synthesis of cortisol, sex steroids
- secretion of large amounts of deoxycorticosterone (DOC) and corticosterone
- decreased aldosterone secretion, suppression of renin

17α-hydroxylase deficiency

- recognized at the time of puberty in young adults

- <u>presenting symptoms:</u>
  - hypertension (↑ DOC, low renin, low aldosterone)
  - hypokalemia
  - primary amenorrhea
  - pseudohermaphroditism
  - cortisol deficiency
- no virilization or retarded growth

11β-hydroxylase deficiency

- mutations of genes on chromosome 8
- recognized in newborns and infants
- classic, mild, late-onset forms (usually mild, with partial defect of cortisol production)
- ↑ androgens, 11-deoxycortisol, DOC, 17-hydroxyprogesterone, urinary 17-ketosteroids and 17-hydroxycorticosteroids
- ↓ cortisol

11β-hydroxylase deficiency

- virilization
- hypertension (↑ DOC, hypokalemia, low renin)
- diagnosis: ↑11-deoxycortisol, DOC, urinary excretion of their metabolites

Androgen and estrogen producing adrenal tumors

- malignancies originating in the zona reticularis
- features of mineralocorticoid excess: hypertension, hypokalemia, renin supression
- inhibition of 11β–hydroxylase with increased production of androgens, DOC, 11-deoxycortisol
- enzymatic inhibition probably is due to high intra-adrenal concentration of androgens (pseudosubstrate for the reaction)

Syndrome of apparent mineralocorticoid excess (11β-hydroxysteroid dehydrogenase deficiency)

- rare disorder
- mutation in gene encoding 11β-hydroxysteroid dehydrogenase type 2, which is present in the renal tubule
- ↓ periperal metabolism of cortisol: impaired conversion to cortisone in the renal tubule → accumulation of cortisol and occupancy of mineralocorticosteroid receptor
- diagnosis: free steroids in urine (cortisol/cortisone) or steroid metabolites
- treatment: spironolactone, eplerenone, triamterene, amiloride

Chronic ingestion of Licorice

- glycyrrhizic acid in Licorice and its metabolite – glycyrrhetinic acid – inhibit 11β-hydroxysteroid dehydrogenase in the kidney (syndrome of apparent mineralocorticoid excess)
- derivative - carbenoxolone (an antigastric ulcer drug)
- symptoms: hypertension, hypokalemia, renal Na retension, volume expansion, suppressed plasma renin activity, metabolic alkalosis

Liddle's syndrome

- familial disorder, autosomal dominant pattern of inheritance
- defect in the epithelial Na channel resulting in constitutive activation
- symptoms: hypertension, hypokalemia, renal K wasting, metabolic alkalosis, suppressed plasma renin activity, low aldosterone
- treatment: administration of amiloride or triamteren (inhibitors of Na channel), salt restriction

Mutations of mineralocorticoid receptor (Geller's syndrome)

- autosomal dominant form of hypertension caused by a mutation in ligand binding domain – partial activation in the absence of aldosterone
- hypertension before the age of 20

Type II pseudohypoaldosteronism (Arnold-Healy-Gordon Syndrome)

- autosomal dominant disorder
- hypertension+hyperkalemia
- low renin, low aldosteron
- impairment of renal K^+ excretion
- mutations in genes encoding kinases that regulate Na^+, Cl^-, K^+ pathways in distal nephron segments
- increased renal NaCl reabsorption with inhibited K^+ secretion
- treatment: severe dietary salt restriction, antihypertensives (especially thiazide diuretics)

Glucocorticoid resistance

- autosomal recessive or dominant
- inactivating mutations of the glucocorticoid receptor gene
- ↑ cortisol and ACTH
- no clinical features of Cushing's syndrome
- permanent ↑ ACTH → production of compounds with mineralocorticoid activity
- ↑ cortisol stimulates mineralocorticoid receptor

Renin-secreting tumors

- very rare
- usually hemangiopericytomas containing juxtaglomerular cells
- other tumors secreting renin: Wilms' tumor, pulmonary tumors
- hypertension, hypokalemia
- high renin+high aldosterone
- diagnosis: biochemical testing, CT, venous sampling

Cushing's syndrome

- chronic glucocorticoid excess
- **ACTH-dependent (90%)**
  - pituitary adenoma (Cushing's disease) – 80%
  - nonpituitary neoplasm (ectopic ACTH secretion) – 10%
- **ACTH-independent (10%)**
  - iatrogenic (glucocorticoids)
  - adrenal neoplasm (adenoma, carcinoma)
  - nodular adrenal hyperplasia

Cushing's syndrome - clinical features

- obesity – central, mainly affecting the face („moon like face"), neck („buffalo hump"), trunk, abdomen, with relative sparing of the extremities

- skin changes – easy bruising, striae (red to purple, most commonly abdominal), acne, slow healing of minor wounds, mucocutaneous fungal infections, hyperpigmentation in case of ectopic ACTH secretion

Cushing's syndrome – clinical features

- hirsutism
- gonadal dysfunction
- psychologic disturbances – emotional lability, anxiety, depression, poor concentration, psychosis
- muscle weakness (more often proximal)
- osteoporosis
- diabetes mellitus
- hypokalemia
- hypertension

Cushing's syndrome – associated hypertension

- hypertension in approximately 80% of cases of endogenous hypercortisolemia (only in 10-20% in case of exogenous)
- night-time RR decline is significantly lower than that in patients with essential hypertension

Cushing's syndrome – associated hypertension

- mechanisms of RR elevation:

- ↑ hepatic production of angiotensinogene
- ↑ cardiac output
- ↓ production of prostaglandins (inhibition of phospholipase A)
- ↑ insulin resistance
- oversaturation of 11β-HSD activity with increased mineralocorticoid effect
- ↑ vascular sensitivity to catecholamines
- ↑ extra- and intravasular volume
- ectopic ACTH production – frequently associated with ↑DOC and corticosterone – mineralcorticosteroid excess state

Cushing's syndrome - diagnosis

- diurnal rhythm of cortisol secretion
- urinary free cortisol (24 h urine collection)
- plasma ACTH
- dexamethasone suppression test:
  - screening test (short test) with 1 mg at bedtime (determination of cortisol at 8.00 a.m. – in healthy subjects < 1.8 μg/dl)
  - low- and high-dose
- pituitary MRI
- inferior pertosal sinus sampling
- CT and MRI of adrenal glands

Cushing's syndrome - treatment

- pituitary adenoma: surgery (transsphenoidal or transcranial), radiation
- ectopic ACTH syndrome: surgery (if possible), drugs that block steroid synthesis (aminoglutethimide, ketoconazole, metyrapone), bilateral adrenalectomy in very severe cases
- adrenal tumors: surgery, mitotane (the drug of choice in case of adrenal carcinoma)

Metabolic syndrome

- characterized by:
- hypertension
- abdominal obesity
- dyslipidemia
- insulin resistance
- insulin resistance - significantly associated with hypertension
- patients with essential hypertension - often insulin resistant

Metabolic syndrome and hypertension

- insulin - direct stimulation of the calcium pump → calcium loss from the cell (in a cell resistant to insulin the insulin-induced calcium loss is decreased)
- increased intracellular calcium → increased vascular smooth muscle cells vasoconstriction
- ↑ sodium retention
- ↑ activity of the adrenergic nervous system
- obesity is associated with ↑production of adipokines that have impact on blood pressure

Hyperparathyroidism and hypertension

- hypercalcemia - associated with ↑ incidence of hypertension
- in patients with primary hyperparathyroidism, hypertension is observed in approximately 40% of cases
- the mechanisms of these associations are unclear (hypercalcemia with ↑ response to catecholamines???)
- hypertension is not cured or better controlled after parathyroidectomy!

Hyperthyroidism and hypertension

↑ systolic blood pressure by:

- ↑ heart rate (tachycardia)
- ↓ systemic vascular resistance
- ↑ cardiac output
- ↑ stroke volume

Hypothyroidism and hypertension

- positive association between serum TSH and blood pressure

<u>hypothyroid patients often have:</u>

- ↑ diastolic blood pressure
- impaired endothelial function
- ↑ systemic vascular resistance
- extracellular volume expansion

subclinical hypothyroidism seems not to be associated with hypertension

Acromegaly and hypertension

- prevalence of hypertension- 46%
- GH - antinatriuretic actions, may lead to sodium retention and volume expansion
- ↑ systolic output and high heart rate (may lead to congestive heart failure)
- the RAAS system appears to be implicated in the pathogenesis of hypertension in patients with acromegaly (↓ PRA, disturbances in dopaminergic regulation of aldosterone secretion)